Carcinogenesis Advance Access published March 16, 2006

Published by Oxford University Press 2006

Title: Polymorphisms in Oxidative Stress Genes and Risk for Non-Hodgkin Lymphoma

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Key words: non-Hodgkin lymphoma, oxidative stress, genetic polymorphism

Written informed consent was obtained from all participants, in accordance with US Department of Health and Human Services guidelines. This study was approved by the institutional review boards at the NIH and at each participating Surveillance Evaluation and End Results (SEER) site (Iowa, Seattle, Los Angeles, and Detroit).

Financial support: Public Health Service (PHS) contracts N01-PC-65064, N01-PC-67008, N01-PC-67009, N01-PC-67010, N02-PC-71105.

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Abstract

Evidence supporting the contribution of oxidative stress to key pathways in cancer, such as inflammation and DNA damage, continues to mount. We investigated variations within genes mediating oxidative stress to determine whether they alter risk for non-Hodgkin lymphoma (NHL). Thirteen single nucleotide polymorphisms (SNPs) from ten oxidative stress genes (*AKR1A1, AKR1C1, CYBA, GPX, MPO, NOS2A, NOS3, OGG1, PPARG, SOD2*) were genotyped in 1,172 NHL cases and 982 population-based controls from a U.S. multi-center case-control study. For NHL and five subtypes (diffuse large B-cell, follicular, marginal zone, small lymphocytic, T-cell), SNP associations were calculated. Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for sex, age (<45, 45-64, 65+ years), race (white, black, other), and study site. Overall, the oxidative stress pathway was associated significantly with the B-cell NHL subtype, diffuse large B-cell (global p-value=0.003). Specifically, for nitric oxide synthase (*NOS2A* Ser608Leu, rs2297518) Leu/Leu homozygotes, there was a two-fold risk increase for NHL (OR=2.2, 95% CI=1.1-4.4) (referent=Ser/Ser and Ser/Leu). This risk increase was consistent by cell lineage (B- and T-cell NHL) and pronounced for the two most common subtypes, diffuse large B-cell (OR=3.4, 95% CI=1.5-7.8) and follicular lymphoma (OR=2.6, 95% CI=1.0-6.8). In an analysis of manganese superoxide dismutase (*SOD2* Val16Ala, rs1799725) Ala/Ala homozygotes, we observed moderately increased risks for B-cell lymphomas (OR=1.3, 95% CI=1.0-1.6; referent=Val/Val and Val/Ala) that was consistent across the B-cell subtypes. Genetic variations that result in an increased generation of reactive oxygen species appear to increase risk for NHL and its major subtypes, particularly diffuse large B-cell lymphoma. Independent replication of our findings are warranted and further evaluation of

oxidative stress in the context of inflammation, DNA repair, and the induction of the NF-kB pathway may further reveal important clues for lymphomagenesis.

Introduction

Identifying exogenous and endogenous sources of inflammation and DNA damage are critically important in understanding cancer etiology. One endogenous source of particular interest is the induction of oxidative stress, defined as a state when levels of free radicals exceed antioxidant defense mechanisms (1). While the generation of free radicals and reactive oxygen species (ROS), including nitric oxide, contributes to a spectrum of normal physiological processes, an excess due to increased production or inefficient elimination of free radicals or ROS can result in DNA and protein damage (2). The presence of oxidative stress has already been implicated in select inflammatory disorders (e.g., chronic gastritis, pancreatitis, inflammatory bowel disease) and cancers associated with these conditions (1;3). It is therefore hypothesized that genetic variations among enzymes that mediate oxidative stress and the generation of ROS could also modulate cancer risk.

Previous investigations of hematopoietic malignancies have identified three candidate genes with known alterations of functional significance in oxidative stress; namely, the *NOS2A* gene which encodes inducible nitric oxide synthase (iNOS), the *SOD2* gene which encodes the enzyme manganese superoxide dismutase (MnSOD), and the *MPO* gene which encodes myeloperoxidase. Briefly, iNOS is an enzyme that can produce high levels of nitric oxide (NO) for prolonged periods of time; although small amounts of nitric oxide (NO) suppresses tumorigenesis by inducing apoptosis (2), sustained high levels of NO results in chronic inflammation. To date, high levels of iNOS expression as well as NO have been demonstrated in human B-cell NHLs (follicular, diffuse large B-cell, and MALT lymphomas) and T-cell leukemias (4-7). The mitochondrial enzyme encoded by the nuclear genome, MnSOD, is a

primary antioxidant that protects cells from superoxide radicals by converting ROS into hydrogen peroxide. Recently, MnSOD activity has been shown to modulate apoptosis and suppress tumorigenesis (8) and accordingly, diminished MnSOD activity has been found in lymphoma tumors (4;7). Finally, myeloperoxidase (MPO), primarily expressed in hematopoietic cells, is a critical enzyme for the production of hypochlorous acid, which contributes to antimicrobial activity (9). Reduced MPO expression has previously been associated with increased risk for adult leukemia, acute myeloid leukemia, and infections (10;11).

Because genetic variations that result in altered enzymatic activity or gene expression for these and other genes important for mediating oxidative stress have previously been reported (12;13), we evaluated a set of common genetic variants with putative functional significance in the risk of non-Hodgkin lymphoma in a large population-based case-control study conducted in the United States. To our knowledge, this is the first multi-gene investigation for main effects of oxidative stress gene polymorphisms in NHL risk. We report results for NHL and for five NHL subtypes (diffuse large B-cell lymphoma, follicular, marginal zone, small lymphocytic lymphoma, and T cell lymphomas).

Methods

Study Population. The study population has previously been described in detail(14). We included 1,321 newly diagnosed NHL cases identified in four Surveillance, Epidemiology, and End Results registries (Iowa; Detroit, MI; Los Angeles, CA; Seattle, WA) aged 20-74 years between July 1998-June 2000 without evidence of HIV infection. 1,057 population controls were identified by random digit dialing (<65 years) and from Medicare eligibility files (≥65 years). Overall participation rates were 76% in cases and 52% in controls; overall response rates were 59% and 44%, respectively. Written informed consent was obtained from each participant prior to interview, in accordance with US Department of Health and Human Services guidelines. This study was approved by the institutional review boards at the NIH and at each participating Surveillance Evaluation and End Results (SEER) site (Iowa, Seattle, Los Angeles, and Detroit). All study participants were asked to provide a venous blood or mouthwash buccal cell sample. We obtained blood samples from 773 cases and 668 controls, and buccal cells from 399 cases and 314 controls. We evaluated the 1,172 cases (89%) and 982 controls (93%) for whom biological samples were obtained for genotyping (Table 1). Genotype frequencies for individuals who provided blood compared to buccal cells were equivalent (15) and a recent report which included data from our present study found no differences in genotype frequencies by participation status (15).

Histopathology. Each registry provided NHL pathology and subtype information derived from abstracted reports by the local diagnosing pathologist. All cases were histologically confirmed and coded according to the International Classification of Diseases for Oncology, 2nd Edition(16). We evaluated the following NHL histologies: (i) NHL overall, (ii) B-cell

lymphomas, (iii) T-cell lymphomas, and four B-cell subtypes: (iv) DLBCL, (v) follicular, (vi) marginal zone, and (vii) small lymphocytic lymphoma (SLL).

Laboratory Methods

DNA extraction. DNA was extracted from blood clots or buffy coats (BBI Biotech, Gaithersburg, MD) using Puregene Autopure DNA extraction kits (Gentra Systems, Minneapolis, MN). DNA was extracted from buccal cell samples by phenol-chloroform extraction methods(17).

Genotyping. We selected thirteen single nucleotide polymorphisms (SNPs) in ten oxidative stress genes (Table 2) based on evidence of putative functional importance and/or evidence of an association with NHL-associated risk conditions (e.g., autoimmune diseases) in animal or human studies. All genotyping was conducted at the National Cancer Institute Core Genotyping Facility (CGF, Advanced Technology Corporation, Gaithersburg, MD) using the Taqman platform. Sequence data and assay conditions are provided at http://snp500cancer.nci.nih.gov.(18) Genotyping results in blood-based DNA samples were analyzed first and further conducted in buccal cell-based DNA when there was sufficient DNA. Successful genotyping was achieved for 96%-100% of DNA samples for all SNPs; the completion rates did not differ by blood- or buccal-based DNA and Hardy-Weinberg Equilibrium (HWE) was observed in the control group for each SNP (assessed separately for non-Hispanic Caucasians and Blacks).

Quality control (QC). 40 replicate samples from each of two blood donors and duplicate samples from 100 study subjects processed in an identical fashion were interspersed for all

genotyping assays and blinded from the laboratory. Agreement for QC replicates and duplicates was ≥99% for all assays. For each plate of 368 samples, genotype-specific QC samples were also included and comprised four homozygote wild-type, four heterozygote, four homozygote variant, and four DNA negative controls.

Statistical Analysis

We calculated odds ratios (OR) as an estimate of the relative risk, and 95% confidence intervals (CI) for each genotype with each NHL histology, using the homozygous wild-type genotype as the referent group. For each histology and genotype, we calculated the p for trend based on the 3-level ordinal variable (0, 1, 2) of homozygote wild-type, heterozygote, and homozygote variant. We also evaluated the dominant model with homozygote wild-type was the referent for comparison to heterozygote and homozygote variants, and the recessive model with homozygote wild-type and heterozygote variants combined and used as a referent group for comparison to homozygote variants.

We first conducted stratified analysis by age (<60 and ≥60 years), gender (male, female) and race (non-Hispanic Caucasians, Blacks). Finding no significant differences in the risk estimates by each of these three strata, we pooled the results and adjusted for age (<54, 55-64, 65+ years), gender (male, female), study site (Iowa, LA, Seattle, Detroit) and race (white, black, other), as these were all design variables. We note that adjustment by finer age strata (e.g., 10 year strata) provided consistent results but less stable statistical models due smaller numbers within each stratum. To further assure that our findings were not a result of population stratification(19), we

also conducted analyses stratified by study site. Although finding no significant differences by study site, we nevertheless retain it in the model as it was a design variable.

To evaluate the robustness of our risk estimates, we computed the false discovery rate (FDR) (Benjamini-Hochberg adjustment)(20), which reflects the expected ratio of false positive findings to the total number of significant findings. The FDR was computed based on an additive model using the p-trends for each genotype which allowed the minimal degrees of freedom and thus comparisons (m=13), for $p<0.05$. For each genotype association with a two-sided p-value<0.05, we also calculated the false positive report probabilities (FPRP)(21) using prior probabilities ranging from 0.01-0.001 based on gene selection criteria described above. A cut-off of 0.2 was used as the threshold for noteworthiness by the FPRP. We assessed the global significance of the association between oxidative stress SNPs evaluated and NHL with the likelihood ratio Chi-square statistics comparing the logistic regression models that included all SNPs as the main effects against the null model that included none of the SNPs.

Results

In all NHL, we observed a doubling in risk (OR=2.2, 95% CI=1.1-4.4, p=0.03) for individuals homozygous for the nonsynonymous SNP in *NOS2A* (Ser608Leu: Leu/Leu, compared to the referent Ser/Ser and Ser/Leu) (Table 3). This risk increase was statistically significant for B-cell lymphomas (OR=2.2, 95% CI=1.1-4.5, p=0.03) and not statistically significantly elevated for T-cell lymphomas (OR=3.1, 95% CI=0.6-15.3, p=0.2). Among B-cell lymphomas, risk for *NOS2A* Leu/Leu homozygotes was pronounced for the two most common subtypes, diffuse large B-cell (OR=3.4, 95% CI=1.5-7.8, p=0.004) and follicular lymphomas (OR=2.6, 95% CI=1.0-6.8, p=0.05) (Table 4). Except for T cell lymphomas, no increased risk was observed for NOS2A Leu/Ser heterozygotes, supporting an overall recessive model for *NOS2A* as described.

There was no association between the *SOD2* (Val16Ala) Val/Ala or Ala/Ala genotypes with NHL overall when compared to the common referent group (*SOD2* Val/Val) (Table 3). However, for *SOD2* Ala/Ala homozgyotes (referent: Val/Val and Val/Ala), there was a statistically significant association with B-cell lymphomas (OR=1.3, 95% CI=1.0-1.6, p=0.01) and among the four B-cell subtypes evaluated, risk elevation was statistically significant for *SOD2* Ala/Ala homozygotes and diffuse large B-cell lymphoma (OR=1.3, 95% CI=1.0-1.8, p=0.05) (Table 4).

We also evaluated risk for *MPO* (-463A) GA and AA genotypes (referent = GG); for all NHL, we found a small risk increase (OR=1.3, 95% CI=1.1-1.5, p=0.01) which was observed for both B-cell and T-cell lymphomas although statistically significant only for B-cell lymphomas (Table 3). Among B-cell subtypes, the increased risk was also significantly observed in diffuse large B-

cell lymphomas (OR=1.3, 95% CI=1.0-1.7, p=0.04). Consistently elevated but not statistically significant risks were observed for follicular (OR=1.2, 95% CI=0.9-1.6, p=0.3), marginal zone (OR=1.5, 95% CI=1.0-2.4, p=0.06) and small lymphocytic lymphoma (OR=1.2, 95% CI=0.8-1.7, p=0.4) (Table 4). All risk increases, however, were driven by the *MPO* GA heterozygote frequencies; in fact, for NHL and all NHL subtypes, the most robust associations were the increased risks observed among *MPO* GA heterozygotes. Evaluation of the *MPO* AA genotype (referent = GG or GA) suggests decreased NHL risk that is consistent across all NHL subtypes evaluated, again driven by frequency differences between cases and controls of the *MPO* GA heterozygotes (Table 3 and 4).

We also report increased risk for follicular lymphoma with the synonymous *PPARG* His477His polymorphism. When compared to the common homozygote variant (CC), we found a 1.3-fold (95% CI=0.9-1.9, p=0.2) increased risk for follicular lymphoma for CT heterozygotes and a 3.0-fold (95% CI-1.2-7.2, p=0.01) increased risk for TT homozygotes (p-trend=0.02) (Table 4).

All aforementioned associations were consistent when restricted to non-Hispanic Caucasians. In addition, significant elevations in risk were also observed when investigating joint effects between genes; likely due to the small numbers of genotypes associated with risk, however, formal tests for interactions were not statistically significant (data not shown). The remaining nine SNPs evaluated in *AKR1A1, AKR1C1, CYBA, GPX1, NOS3*, and *OGG1* were not significantly associated with NHL or any subtype (Online Supplemental Tables 1 and 2). In the overall evaluation of the oxidative stress pathway, we find a global test for significance at

p=0.003 for the B-cell subtype diffuse large B-cell lymphoma. The global test for significance was greater than 0.05 for all NHL and all other subtypes evaluated.

Discussion

In our investigation of thirteen common SNPs chosen because of putative functional importance drawn from key genes in the oxidative stress pathway, we report that variations in *NOS2A, SOD2*, *MPO,* and *PPARG* appear to alter risk for NHL. Although some risk estimates were modest, the overall global test for significance does support further pursuit of the oxidative stress pathway particularly for DLBCL. Confirmation of our results in an independent study is warranted and further identification of critical genes in the oxidative stress pathway associated with NHL and its subtypes could yield important clues to lymphomagenesis as it relates to inflammation and DNA damage.

NOS2A (Ser608Leu) Leu/Leu homozygotes have been reported to confer higher enzymatic activity and inducible nitric oxide synthase (iNOS) expression (22;23), resulting in increased NO production and inflammation. This is substantiated by *TP53* and *NOS2* knock-out mice where high levels of anti-inflammatory cytokines that suppress tumorigenesis are found (24). The increased risks we observed for *NOS2A* homozygotes were notable particularly for their consistency of association; in addition to increased risk for NHL, the association was consistent by cell lineage (B and T cell lymphomas) and for the major subtypes diffuse large B cell and follicular lymphoma. Our results are consistent with previous reports that demonstrate iNOS expression in various hematopoietic malignancies, including diffuse large B-cell lymphomas and adult T-cell leukemias (6;25;26). Since the production of endogenous NO results in pro-

inflammatory cytokine expression including that from *TNF* (27), a gene that has previously been associated with increased NHL risk (28), we suggest that an oxidative stress state leading to chronic inflammation could contribute to lymphomagenesis. Although we did not identify further associations with *NOS3* polymorphisms, *NOS2A* produces much higher levels of NO and resulting cytotoxicity(29) compared to the endothelial NOS (eNOS) encoded by *NOS3*.

Expression of manganese superoxide dismutase (MnSOD) plays a critical role in protecting cells from free radicals and oxidative damage(30) but high expression has been found to be deleterious and in particular, further induced by pro-inflammatory cytokines such as *TNF*. The functional evidence for the *SOD2* (Val16Ala) nonsynonymous polymorphism within a signal sequence of the protein coding region has not yet been clarified (31;32). In our data, we find the rare *SOD2* Ala/Ala homozygote genotype modestly associated with increased risk for all NHL and its subtypes. This association is consistent with some but not all previous reports for other cancers(33-44). Among hematopoietic cells, total superoxide dismutase activity has been reportedly increased in myelocytic, monocytic and lymphocytic leukemia cells and significantly elevated in leukocytes isolated from patients with malignant lymphomas (45). However, the role of superoxide dismutase activity remains unclear as deficient activity has also been reported in malignant lymphomas (4) and some animal studies have demonstrated reduced MnSOD activity with DNA damage and cancer incidence (13). Further clarification of the role of this gene is therefore required.

MPO is a lysosomal enyme important in neutrophils and monocytes that produces a potent oxidant, hypochlorous acid as well as other reactive oxygen species, which have antimicrobial

activity against a wide range of organisms (9). The unchecked production of hypochlorous acid and metabolism of other exogenous substances (e.g., benzo[a]pyrene) into free radicals, however, contributes to oxidative stress and subsequent inflammation (46). The *MPO* -463A allele confers a 25-fold decreased MPO expression in vitro (47)and has been found associated with a decreased risk for a number of tumors(33;35) and the high activity allele (G) has been associated with increased risk for acute myeloid leukemia (48). In our data, the GA heterozygote was associated with increased NHL risk that was consistent by cell lineage and for all major NHL subtypes. This puzzling finding drove the observed decreased risk for the AA genotype as shown for other tumors(35;49). Interestingly, this increased risk among GA heterozygotes is similarly found in previously published reports for other tumors(33;35;50). It is plausible that given the dual role of MPO as an antimicrobial agent and as a regulator of inflammation, an independent association might be difficult to tease apart without the presence of the requisite exposure.

Peroxisome proliferator activated receptor-gamma2 (PPARgamma2) has been linked to the production of reactive oxygen species and PPARγ agonists have recently been shown to inhibit NF-kB and its downstream consequences of inflammation(51). It is possible that the synonymous exon 10 *PPARγ* polymorphism we evaluated either alters stability of the transcript (52) or it is in linkage disequilibrium with the causal variant. Its modest association with follicular lymphoma in a dose-dependent manner supports a role for oxidative stress in this lymphoma subtype.

To our knowledge, this is the first molecular epidemiologic study to evaluate the association between polymorphisms in oxidative stress genes and risk for NHL. Study strengths include our large sample size for which the associations for each genetic polymorphism could be measured. We believe the accuracy of our genotyping data minimized misclassification, enhancing our ability to detect small effects. Limitations of our study include loss of eligible subjects to death, illness, and refusal to participate, limited power to test for interaction and the potential for false positive findings. However, a recent report which included data from our present study found no differences in genotype frequencies by participation status (15). Further, although it is conceivable that individuals participating in the present study are related to survival, preliminary analyses reveal the survival patterns of our cases to be consistent with that of the general population. Only for the *NOS2A* Leu/Leu genotype which was assigned a prior probability of 0.01 was the false positive report probability notable with a <20% chance of being a false positive. Adjustments for multiple comparisons by FDR, however, did not yield significant associations; further adjustment which considered all modes of inheritance also did not yield significant associations. Because we did not have adequate power to detect modest associations for rare genotypes and less common subtypes, replication of our findings and analysis of extended haplotypes to identify additional variants of importance are warranted.

In summary, we believe our results support a role for the induction of an oxidative stress state in lymphomagenesis. Our results warrant replication in further studies and detailed haplotype analysis with htSNPs as other polymorphisms may be important as well as the allegedly functional ones we have reported. A detailed evaluation of oxidative stress genes particularly as they relate to the inflammation, the NF-kB pathway, and DNA damage is justified and large

pooled studies that facilitate the evaluation of multiple SNP with NHL subtypes would be optimal in advancing this line of research (28).

Acknowledgements: This research was supported by the Intramural Research Program of the NIH, National Cancer Institute.

Tables and Figures

Table 1. Characteristics of study participants (n=2,154) who provided blood or buccal cell samples for genotyping.

Table 2. Oxidative stress genes and single nucleotide polymorphisms evaluated in the NCI-SEER multi-center case-control study for non-Hodgkin lymphoma.

Table 3. Distribution of *NOS2A*, *SOD2*, *MPO,* and *PPARG* genotypes among all NHL, B- and T-cell lymphoma cases and controls and odds ratios adjusted for age, race, sex, and study site.

Table 4. Distribution of *NOS2A*, *SOD2*, *MPO,* and *PPARG* genotypes among diffuse, follicular, marginal zone and small lymphocytic lymphoma cases and controls and odds ratios adjusted for age, race, sex, and study site.

Online Supplemental Table 1. Distribution of remaining genotypes among all NHL, B- and T-cell lymphoma cases and controls and odds ratios adjusted for age, race, sex, and study site.

Online Supplemental Table 2. Distribution of remaining genotypes among DLBCL, follicular, SLL and marginal zone lymphoma cases and controls and odds ratios adjusted for age, race, sex, and study site.

Table 1. Characteristics of study participants (n=2,154) who provided blood or buccal cell samples for genotyping.

Characteristic		NHL Cases (n=1,172)	Controls (n=982)	p value***
		n (%)	n (%)	
Age at enrollment (years)	<35	65 (6%)	55 (6%)	0.0017
	35-44	148 (13%)	97 (10%)	
	45-54	254 (22%)	185 (19%)	
	55-64	319 (27%)	240 (24%)	
	65+	386 (33%)	405 (41%)	
Sex	Male	643 (55%)	516 (53%)	0.28
	Female	529 (45%)	466 (47%)	
Race	Caucasian	1006 (86%)	787 (80%)	<0.0001
	Non-Hispanic	966 (82%)	747 (76%)	
	Hispanic	38 (3%)	28 (3%)	
	African-American	82 (7%)	130 (13%)	
	Other/unknown	84 (7%)	65 (7%)	
Study center	Detroit	241 (21%)	173 (18%)	0.26
	Iowa	338 (29%)	281 (29%)	
	Los Angeles	295 (25%)	251 (26%)	
	Seattle	298 (25%)	277 (28%)	
Biospecimen collected	Blood	759 (65%)	662 (67%)	0.20
	Buccal cells	399 (34%)	314 (32%)	
	Blood and buccal cells	14 (1%)	6 (1%)	
DNA source	Blood	773 (66%)	668 (68%)	0.31
	Buccal cells	399 (34%)	314 (31%)	
Case pathology	All B cell	955 (81%)	-	-
	Diffuse large B-cell	371 (32%)	-	
	Follicular	280 (24%)	-	
	SLL*	148 (13%)	-	
	Marginal Zone**	95 (8%)	-	
	Mantle Cell	43 (4%)	-	
	Burkitt	18 (1%)	-	
	All T cell	73 (6%)	-	
	NOS	144 (12%)	-	

*includes chronic lymphocytic leukemia, lymphoplasmacytic (n=28); ** MALT (n=62), marginal zone (n=33); ***p-value for Pearson chi-square statistic.

Table 2. Oxidative stress genes and single nucleotide polymorphisms evaluated in the NCI-SEER multicenter case-control study for non-Hodgkin lymphoma.

Gene	Name	Chromosomal Location	SNP rs #	Nucleotide change	Amino acid change
AKR1A1	aldo-keto reductase family 1, member A1	1p33-p32	rs2088102	IVS5+282T>C	
AKR1C1	aldo-keto reductase family 1, member C1	10p15-p14	rs8483	Ex9+68A>G	
CYBA	cytochrome b-245, alpha polypeptide	16q24	rs4673	Ex4+11T>C	Tyr72His
			rs1049255	Ex6-41C>T	
			rs7195830	Ex6-16A>G	
GPX1	glutathione peroxidase 1	3p21.3	rs1050450	Ex1-226C>T	Pro200Leu
MPO	myeloperoxidase	17q23.1	rs2333227	-642G>A, aka -463A	
NOS2A	nitric oxide synthase 2A	17cen-q11.2	rs2297518	Ex16+14C>T	Ser608Leu
NOS3	nitric oxide synthase 3	7q36	rs1799983	Ex8-63G>T	Glu298Asp
			rs2070744	IVS1-762C>T [-786]	
OGG1	8-oxoguanine DNA glycosylase	3p26.2	rs1052133	Ex6-315C>G	Ser326Cys
PPARG	peroxisome proliferative activated receptor, gamma	3p25	rs3856806	Ex10+161C>T	His477His
SOD2	superoxide dismutase 2, mitochondrial	6q25.3	rs1799725	Ex2+24T>C	Val16Ala

Table 3. Distribution of *NOS2A*, *SOD2*, *MPO,* and *PPARG* genotypes among all NHL, B- and T-cell lymphoma cases and controls and odds ratios adjusted for age, race, sex, and study site.

		Controls	All NHL			B cell NHL			T cell NHL		
Gene	**Genotype**	**n (%)**	**n (%)**	**OR (95% CI)**	**p value**	**n (%)**	**OR (95% CI)**	**p value**	**n (%)**	**OR (95% CI)**	**p value**
NOS2A	Ser/Ser	422 (67)	493 (66)	1.0 (ref)	-	417 (68)	1.0 (ref)	-	27 (54)	1.0 (ref)	-
rs2297518	Ser/Leu	194 (31)	223 (30)	1.0 (0.8-1.2)	0.9	175 (28)	0.9 (0.7-1.2)	0.5	21 (42)	1.7 (0.9-3.2)	0.09
Ser608Leu	Leu/Leu	11 (2)	30 (4)	**2.2 (1.1-4.4)**	**0.03**	25 (4)	**2.1 (1.0-4.4)**	**0.04**	2 (4)	3.7 (0.7-19.0)	0.1
	Ser/Leu or Leu/Leu	205 (33)	253 (34)	1.1 (0.8-1.3)	0.6	200 (32)	1.0 (0.8-1.2)	0.9	23 (46)	**1.8 (1.0-3.3)**	**0.05**
				p-trend=	0.3		p-trend=	0.6		**p-trend=**	**0.03**
	Ser/Ser or Ser/Leu	616 (98)	716 (96)	1.0 (ref)	-	592 (96)	1.0 (ref)	-	48 (96)	1.0 (ref)	-
	Leu/Leu	11 (2)	30 (4)	**2.2 (1.1-4.4)**	**0.03**	25 (4)	**2.2 (1.1-4.5)**	**0.03**	2 (4)	3.1 (0.6-15.3)	0.2
SOD2	Val/Val	240 (26)	285 (25)	1.0 (ref)	-	230 (25)	1.0 (ref)	-	26 (37)	1.0 (ref)	-
rs1799725	Val/Ala	486 (52)	545 (49)	0.9 (0.7-1.1)	0.4	431 (47)	0.9 (0.7-1.1)	0.3	30 (42)	0.6 (0.3-1.0)	0.06
Val16Ala	Ala/Ala	211 (23)	290 (26)	1.1 (0.9-1.4)	0.5	247 (27)	1.2 (0.9-1.5)	0.2	15 (21)	0.6 (0.3-1.0)	0.2
	Val/Ala or Ala/Ala	697 (55)	835 (75)	1.0 (0.8-1.2)	0.4	678 (74)	1.0 (0.8-1.2)	0.8	45 (63)	0.6 (0.4-1.0)	0.06
				p-trend=	0.5		p-trend=	0.2		p-trend=	0.1
	Val/Val or Val/Ala	726 (78)	830 (74)	1.0 (ref)	-	661 (72)	1.0 (ref)	-	56 (79)	1.0 (ref)	-
	Ala/Ala	211 (23)	290 (26)	1.2 (0.9-1.4)	0.1	247 (27)	**1.3 (1.0-1.6)**	**0.01**	15 (21)	0.9 (0.5-1.6)	0.6
MPO	GG	582 (64)	650 (60)	1.0 (ref)	-	529 (60)	1.0 (ref)	-	39 (55)	1.0 (ref)	-
rs2333227	GA	273 (30)	385 (36)	**1.3 (1.1-1.6)**	**0.005**	311 (36)	**1.3 (1.1-1.6)**	**0.009**	29 (41)	**1.7 (1.0-2.8)**	**0.05**
-463A	AA	50 (6)	47 (4)	0.9 (0.6-1.4)	0.7	36 (4)	0.9 (0.5-1.3)	0.5	3 (4)	1.0 (0.3-3.4)	0.9
	GA or AA	323 (36)	432 (40)	**1.3 (1.1-1.5)**	**0.01**	347 (40)	**1.3 (1.0-1.5)**	**0.03**	32 (45)	1.6 (0.9-2.6)	0.08
				p-trend=	0.08		p-trend=	0.2		p-trend=	0.2
	GG or GA	855 (94)	1035 (96)	1.0 (ref)	-	840 (96)	1.0 (ref)	-	68 (96)	1.0 (ref)	-
	AA	50 (6)	47 (4)	0.8 (0.6-1.3)	0.4	36 (4)	0.8 (0.5-1.2)	0.3	3 (4)	0.8 (0.2-2.7)	0.7
PPARG	CC	459 (75)	537 (76)	1.0 (ref)	-	442 (76)	1.0 (ref)	-	38 (79)	1.0 (ref)	-
rs3856806	CT	137 (22)	150 (21)	0.9 (0.7-1.2)	0.5	126 (22)	0.9 (0.7-1.2)	0.6	9 (19)	0.8 (0.4-1.7)	0.6
His477His	TT	13 (2)	18 (3)	1.1 (0.5-2.3)	0.8	17 (3)	1.3 (0.6-2.7)	0.5	1 (2)	0.8 (0.1-7.0)	0.9
	CT or TT	150 (25)	168 (24)	0.9 (0.7-1.2)	0.6	143 (24)	1.0 (0.8-1.3)	0.8	10 (21)	0.8 (0.4-1.7)	0.6
				p-trend=	0.7		p-trend=	0.9		p-trend=	0.6

Table 4. Distribution of *NOS2A*, *SOD2*, *MPO,* and *PPARG* genotypes among diffuse, follicular, marginal zone and small lymphocytic lymphoma cases and controls and odds ratios adjusted for age, race, sex, and study site.

Genotype		Controls	DLBCL			Follicular			Marginal Zone			SLL		
		n (%)	n (%)	OR (95% CI)	p value	n (%)	OR (95% CI)	p value	n (%)	OR (95% CI)	p value	n (%)	OR (95% CI)	p value
NOS2A	Ser/Ser	422 (67)	139 (66)	1.0 (ref)	-	125 (66)	1.0 (ref)	-	54 (78)	1.0 (ref)	.	70 (65)	1.0 (ref)	-
rs2297518	Ser/Leu	194 (31)	60 (28)	0.9 (0.7-1.3)	0.6	52 (28)	0.9 (0.6-1.3)	0.6	14 (20)	0.6 (0.2-1.2)	0.2	36 (33)	1.1 (0.7-1.7)	0.8
Ser608Leu	Leu/Leu	11 (2)	13 (6)	**3.3 (1.4-7.7)**	**0.005**	8 (4)	2.5 (1.0-6.6)	0.06	1 (1)	0.6 (0.1-5.2)	0.7	2 (2)	1.3 (0.3-5.9)	0.8
	Ser/Leu or Leu/Leu	205 (33)	73 (34)	1.1 (0.8-1.5)	0.8	60 (32)	1.0 (0.7-1.4)	0.9	15 (21)	0.6 (0.4-1.2)	0.2	38 (35)	1.1 (0.7-1.7)	0.7
				p-trend=	0.2		p-trend=	0.6		p-trend=	0.2		p-trend=	0.7
	Ser/Ser or Ser/Leu	616 (98)	199 (94)	1.0 (ref)	-	177 (96)	1.0 (ref)		68 (99)	1.0 (ref)	-	106 (98)	1.0 (ref)	
	Leu/Leu	11 (2)	13 (6)	**3.4 (1.5-7.8)**	**0.004**	8 (4)	**2.6 (1.0-6.8)**	**0.05**	1 (1)	0.7 (0.1-5.8)	0.7	2 (2)	1.2 (0.3-5.7)	0.8
SOD2	Val/Val	240 (26)	75 (22)	1.0 (ref)	-	74 (28)	1.0 (ref)	-	22 (24)	1.0 (ref)	-	41 (28)	1.0 (ref)	-
rs1799725	Val/Ala	486 (52)	174 (50)	1.1 (0.8-1.5)	0.5	123 (46)	0.8 (0.6-1.1)	0.2	40 (44)	0.9 (0.5-1.5)	0.6	67 (46)	0.8 (0.5-1.3)	0.4
Val16Ala	Ala/Ala	211 (23)	98 (28)	**1.4 (1.0-2.0)**	**0.05**	69 (26)	1.0 (0.7-1.5)	0.9	29 (32)	1.4 (0.8-2.6)	0.2	37 (25)	1.0 (0.6-1.7)	0.9
	Val/Ala or Ala/Ala	697 (75)	272 (78)	1.2 (0.9-1.6)	0.2	92 (72)	0.9 (0.6-1.2)	0.3	69 (76)	1.0 (0.6-1.7)	0.9	104 (71)	0.9 (0.6-1.3)	0.5
				p-trend=	0.05		p-trend=	0.9		p-trend=	0.2		p-trend=	0.9
	Val/Val or Val/Ala	726 (78)	249 (72)	1.0 (ref)	-	197 (74)	1.0 (ref)		62 (68)	1.0 (ref)	-	108 (75)	1.0 (ref)	
	Ala/Ala	211 (23)	98 (28)	**1.3 (1.0-1.8)**	**0.05**	69 (26)	1.2 (0.9-1.6)	0.3	29 (32)	1.6 (1.0-2.5)	0.06	37 (25)	1.2 (0.8-1.7)	0.5
MPO	GG	582 (64)	198 (60)	1.0 (ref)	-	157 (62)	1.0 (ref)	-	50 (56)	1.0 (ref)	.	86 (61)	1.0 (ref)	-
rs2333227	GA	273 (30)	122 (37)	**1.4 (1.1-1.9)**	**0.01**	90 (35)	1.3 (0.9-1.7)	0.1	37 (41)	**1.7 (1.1-2.7)**	**0.02**	42 (30)	1.1 (0.7-1.6)	0.7
-463A	AA	50 (6)	12 (3)	0.7 (0.4-1.4)	0.3	8 (3)	0.6 (0.3-1.4)	0.2	3 (3)	0.8 (0.2-2.6)	0.7	12 (9)	1.9 (0.9-3.7)	0.07
	GA or AA	323 (36)	134 (40)	**1.3 (1.0-1.7)**	**0.04**	98 (38)	1.2 (0.9-1.6)	0.3	40 (44)	1.5 (1.0-2.4)	0.06	54 (39)	1.2 (0.8-1.7)	0.4
				p-trend=	0.2		p-trend=	0.7		p-trend=	0.2		p-trend=	0.2
	AA or GA	323 (36)	134 (40)	1.0 (ref)	-	98 (38)	1.0 (ref)	-	40 (44)	1.0 (ref)	-	54 (39)	1.0 (ref)	-
	GG	582 (64)	198 (60)	0.6 (0.3-1.2)	0.2	157 (62)	0.6 (0.3-1.3)	0.2	50 (56)	0.6 (0.2-2.1)	0.4	86 (61)	1.8 (0.9-3.6)	0.08
PPARG	CC	459 (75)	150 (76)	1.0 (ref)		121 (68)	1.0 (ref)		54 (83)	1.0 (ref)		87 (84)	1.0 (ref)	
rs3856806	CT	137 (22)	46 (23)	1.0 (0.7-1.5)	0.9	48 (27)	1.3 (0.9-1.9)	0.2	9 (14)	0.6 (0.3-1.2)	0.2	14 (14)	**0.5 (0.3-0.9)**	**0.03**
His477His	TT	13 (2)	1 (1)	0.2 (0.0-1.5)	0.1	10 (6)	**3.0 (1.2-7.2)**	**0.01**	2 (3)	1.3 (0.3-6.4)	0.7	2 (2)	0.8 (0.2-3.8)	0.8
	CT or TT	150 (25)	47 (24)	0.9 (0.6-1.4)	0.7	58 (32)	1.4 (1.0-2.1)	0.06	11 (17)	0.7 (0.3-1.3)	0.2	16 (15)	**0.5 (0.3-0.9)**	**0.03**
				p-trend=	0.4		**p-trend=**	**0.02**		p-trend=	0.3		**p-trend=**	**0.05**

Online Supplemental Table 1. Distribution of remaining genotypes among all NHL, B- and T-cell NHL cases and controls and odds ratios adjusted for age, race, sex, and study site.

SNP	Genotype	Controls		All NHL				B cell NHL					T cell NHL				
		N	(%)	N (%)	OR	(95% CI)	p	N	(%)	OR	(95% CI)	p	N	(%)	OR	(95% CI)	p
AKR1A1	TT	164	(26)	196 (26)	1.0	(ref)	.	162	(26)	1.0	(ref)		13	(26)	1.0	(ref)	
rs2088102	CT	313	(49)	395 (53)	1.0	(0.8-1.3)	0.8	321	(52)	1.0	(0.8-1.3)	0.8	27	(54)	1.0	(0.5-2.1)	0.9
	CC	156	(25)	159 (21)	0.8	(0.6-1.1)	0.2	137	(22)	0.9	(0.6-1.2)	0.4	10	(20)	0.7	(0.3-1.6)	0.3
	CT or CC	469	(74)	554 (74)	1.0	(0.7-1.2)	0.7	458	(74)	1.0	(0.7-1.2)	0.8	37	(74)	0.9	(0.5-1.8)	0.8
						P-trend=	0.2				P-trend=	0.4				P-trend=	0.4
AKR1C1	GG	228	(38)	282 (41)	1.0	(ref)		239	(42)	1.0	(ref)		19	(42)	1.0	(ref)	
rs8483	AG	287	(48)	316 (46)	0.9	(0.7-1.1)	0.3	260	(46)	0.9	(0.7-1.1)	0.2	18	(40)	0.7	(0.3-1.3)	0.3
	AA	82	(14)	90 (13)	0.9	(0.6-1.3)	0.6	71	(12)	0.9	(0.6-1.2)	0.4	8	(18)	1.2	(0.5-3.0)	0.7
	AG or AA	369	(62)	406 (59)	0.9	(0.7-1.1)	0.3	331	(58)	0.9	(0.7-1.1)	0.2	26	(58)	0.8	(0.4-1.5)	0.4
						P-trend=	0.4				P-trend=	0.3				P-trend=	0.9
CYBA	CC	385	(42)	473 (43)	1.0	(ref)	.	388	(43)	1.0	(ref)		24	(35)	1.0	(ref)	
rs4673	CT	412	(44)	497 (45)	1.0	(0.8-1.2)	0.9	394	(44)	1.0	(0.8-1.2)	0.7	35	(51)	1.4	(0.8-2.5)	0.2
	TT	128	(14)	137 (12)	0.9	(0.7-1.2)	0.4	118	(13)	1.0	(0.7-1.3)	0.7	9	(13)	1.0	(0.4-2.2)	0.9
	CT or TT	540	(58)	634 (57)	1.0	(0.8-1.2)	0.7	512	(57)	1.0	(0.8-1.2)	0.7	44	(65)	1.3	(0.8-2.2)	0.3
						P-trend=	0.5				P-trend=	0.7				P-trend=	0.7
CYBA	AA	155	(26)	179 (26)	1.0	(ref)	-	155	(27)	1.0	(ref)		7	(15)	1.0	(ref)	
rs1049255	AG	284	(48)	329 (48)	1.0	(0.8-1.3)	0.9	270	(47)	1.0	(0.7-1.3)	0.8	23	(50)	1.7	(0.7-4.1)	0.2
	GG	147	(25)	176 (26)	1.0	(0.8-1.4)	0.8	145	(25)	1.0	(0.7-1.4)	0.9	16	(35)	2.2	(0.8-5.5)	0.2
	AG or GG	431	(74)	505 (74)	1.0	(0.8-1.3)	0.9	415	(73)	1.0	(0.7-1.3)	0.8	39	(85)	1.9	(0.8-4.3)	0.1
						P-trend=	0.8				P-trend=	0.9				P-trend=	0.1
CYBA	CC	242	(42)	290 (42)	1.0	(ref)	-	240	(41)	1.0	(ref)		21	(46)	1.0	(ref)	
rs7195830	CT	268	(46)	311 (45)	1.0	(0.8-1.2)	0.7	261	(45)	1.0	(0.7-1.2)	0.7	17	(37)	0.8	(0.4-1.5)	0.5
	TT	73	(13)	96 (14)	1.1	(0.7-1.5)	0.8	78	(13)	1.0	(0.7-1.5)	0.9	8	(17)	1.2	(0.5-3.0)	0.7
	CT or TT	341	(59)	407 (58)	1.0	(0.8-1.2)	0.8	339	(59)	1.0	(0.8-1.2)	0.8	25	(54)	0.9	(0.5-1.7)	0.7
						P-trend=	0.9				P-trend=	0.9				P-trend=	0.9
GPX1	CC	291	(46)	360 (49)	1.0	(ref)	.	297	(49)	1.0	(ref)		22	(43)	1.0	(ref)	
rs1050450	CT	284	(45)	310 (42)	0.9	(0.7-1.1)	0.3	258	(42)	0.9	(0.7-1.1)	0.4	22	(43)	1.1	(0.6-2.1)	0.7
	TT	61	(10)	70 (9)	0.9	(0.6-1.4)	0.8	56	(9)	0.9	(0.6-1.4)	0.7	7	(14)	1.6	(0.6-4.0)	0.3
	CT or TT	345	(54)	380 (51)	0.9	(0.7-1.1)	0.3	314	(51)	0.9	(0.7-1.1)	0.4	29	(57)	1.2	(0.7-2.2)	0.5
						P-trend=	0.4				P-trend=	0.4				P-trend=	0.4

NOS3	GG	300	(50)	343 (47)	1.0	(ref)	.	282	(47)	1.0	(ref)		24	(49)	1.0	(ref)	
rs1799983	GT	244	(41)	318 (44)	1.1	(0.9-1.4)	0.3	272	(45)	1.2	(0.9-1.5)	0.2	19	(39)	1.0	(0.5-1.9)	0.9
	TT	55	(9)	65 (9)	1.0	(0.7-1.5)	0.9	49	(8)	0.9	(0.6-1.4)	0.6	6	(12)	1.5	(0.6-4.0)	0.4
	GT or TT	299	(50)	383 (53)	1.1	(0.9-1.4)	0.4	321	(53)	1.1	(0.9-1.4)	0.4	25	(51)	1.1	(0.6-2.0)	0.8
						P-trend=	0.6				P-trend=	0.7				P-trend=	0.5
NOS3	TT	264	(43)	297 (42)	1.0	(ref)	.	236	(40)	1.0	(ref)		23	(48)	1.0	(ref)	
rs1799983	CT	250	(41)	315 (44)	1.1	(0.9-1.4)	0.4	270	(46)	1.2	(0.9-1.5)	0.2	19	(40)	0.9	(0.5-1.7)	0.7
	CC	97	(16)	97 (14)	0.9	(0.6-1.2)	0.3	80	(14)	0.9	(0.6-1.2)	0.4	6	(13)	0.6	(0.2-1.6)	0.3
	CT or CC	347	(57)	412 (58)	1.0	(0.8-1.3)	0.3	350	(60)	1.1	(0.9-1.4)	0.5	25	(52)	0.8	(0.4-1.5)	0.5
						P-trend=	0.6				P-trend=	0.8				P-trend=	0.4
OGG1	CC	549	(59)	612 (55)	1.0	(ref)	.	501	(55)	1.0	(ref)		38	(55)	1.0	(ref)	
rs1052133	CG	324	(35)	438 (39)	1.2	(1.0-1.4)	0.1	355	(39)	1.2	(1.0-1.4)	0.1	27	(39)	1.1	(0.7-1.9)	0.6
	GG	58	(6)	63 (6)	0.9	(0.6-1.4)	0.7	46	(5)	0.8	(0.6-1.3)	0.4	4	(6)	0.8	(0.2-2.3)	0.6
	CG or GG	382	(41)	501 (45)	1.1	(0.9-1.4)	0.2	401	(44)	1.1	(0.9-1.3)	0.2	31	(45)	1.1	(0.6-1.8)	0.8
						P-trend=	0.4				P-trend=	0.6				P-trend=	0.9

Online Supplemental Table 2. Distribution of remaining genotypes among diffuse, follicular, marginal zone and small lymphocytic lymphoma cases and controls and odds ratios adjusted for age, race, sex, and study site.

		Controls		DLBCL					Follicular					Marginal Zone					SLL				
		N	(%)	N	(%)	OR	(95% CI)	p	N	(%)	OR	(95% CI)	p	N	(%)	OR	(95% CI)	p	N	(%)	OR	(95% CI)	p
AKR1A1	TT	164	(26)	51	(24)	1.0	(ref)	.	50	(27)	1.0	(ref)	.	20	(29)	1.0	(ref)		30	(28)	1.0	(ref)	
rs2088102	CT	313	(49)	115	(54)	1.2	(0.8-1.7)	0.4	96	(51)	1.0	(0.7-1.5)	0.9	37	(54)	0.9	(0.5-1.6)	0.7	53	(49)	1.0	(0.6-1.6)	0.9
	CC	156	(25)	47	(22)	1.0	(0.6-1.5)	0.9	41	(22)	0.9	(0.6-1.5)	0.7	12	(17)	0.5	(0.2-1.2)	0.1	25	(23)	0.9	(0.5-1.6)	0.7
	CT or CC	469	(74)	162	(76)	1.1	(0.8-1.6)	0.6	137	(73)	1.0	(0.7-1.4)	0.9	49	(71)	0.8	(0.4-1.4)	0.4	78	(72)	0.9	(0.6-1.5)	0.8
							p-trend=	0.9				p-trend=	0.7				p-trend=	0.1				p-trend=	0.7
AKR1C1	AA	228	(38)	79	(41)	1.0	(ref)	.	86	49	1.0	(ref)	.	24	(39)	1.0	(ref)	.	37	(37)	1.0	(ref)	.
rs8483	AG	287	(48)	91	(47)	0.9	(0.6-1.3)	0.6	72	41	0.7	(0.5-1.0)	0.03	29	(47)	1.0	(0.6-1.9)	0.9	46	(46)	0.9	(0.6-1.5)	0.7
	GG	82	(14)	22	(11)	0.8	(0.5-1.4)	0.5	18	10	0.6	(0.3-1.1)	0.11	9	(15)	0.9	(0.4-2.1)	0.8	16	(16)	1.3	(0.7-2.4)	0.5
	AA or GG	369	(62)	113	(59)	0.9	(0.6-1.2)	0.5	90	51	0.7	(0.5-0.9)	0.02	38	(61)	1.0	(0.6-1.7)	0.9	62	(62)	1.0	(1.0-0.6)	0.9
							p-trend=	0.4				p-trend=	0.03				p-trend=	0.9				p-trend=	0.6
CYBA	CC	385	(42)	146	(42)	1.0	(ref)	.	110	(42)	1.0	(ref)	.	40	(44)	1.0	(ref)	.	66	(46)	1.0	(ref)	.
rs4673	CT	412	(44)	146	(42)	0.9	(0.7-1.2)	0.7	120	(46)	1.0	(0.8-1.4)	0.8	38	(42)	0.9	(0.6-1.5)	0.8	65	(45)	0.9	(0.6-1.4)	0.7
	TT	128	(14)	53	(15)	1.1	(0.7-1.6)	0.7	32	(12)	0.9	(0.6-1.4)	0.6	13	(14)	1.1	(0.5-2.1)	0.8	13	(9)	0.6	(0.3-1.1)	0.1
	CT or TT	540	(58)	199	(58)	1.0	(0.8-1.3)	0.9	152	(58)	1.0	(0.8-1.3)	0.9	51	(56)	1.0	(0.6-1.5)	0.9	78	(54)	0.8	(0.6-1.2)	0.4
							p-trend=	0.9				p-trend=	0.8				p-trend=	0.9				p-trend=	0.1
CYBA	AA	155	(26)	60	31	1.0	(ref)	.	45	26	1.0	(ref)	.	18	(30)	1.0	(ref)	.	18	(18)	1.0	(ref)	.
rs1049255	AG	284	(48)	91	47	0.8	(0.6-1.2)	0.37	84	48	1.0	(0.7-1.6)	0.8	25	(42)	0.8	(0.4-1.4)	0.4	51	(51)	1.6	(0.9-2.8)	0.1
	GG	147	(25)	43	22	0.8	(0.5-1.2)	0.25	47	27	1.1	(0.7-1.8)	0.7	17	(28)	1.0	(0.5-2.0)	0.9	30	(30)	1.8	(0.9-3.4)	0.07
	AG or GG	431	(74)	134	69	0.8	(0.6-1.2)	0.26	131	74	1.1	(0.7-1.6)	0.7	42	(70)	0.8	(0.5-1.5)	0.5	81	(81)	1.6	(0.9-2.8)	0.08
							p-trend=	0.24				p-trend=	0.7				p-trend=	0.9				p-trend=	0.08
CYBA	CC	242	(42)	78	40	1.0	(ref)	.	73	(41)	1.0	(ref)	.	32	(52)	1.0	(ref)	.	39	(39)	1.0	(ref)	.
rs7195830	CT	268	(46)	97	49	1.1	(0.8-1.5)	0.69	78	(44)	0.9	(0.6-1.3)	0.6	23	(37)	0.7	(0.4-1.2)	0.2	46	(46)	1.1	(0.7-1.7)	0.8
	TT	73	(13)	21	11	0.8	(0.5-1.4)	0.51	28	(16)	1.1	(0.7-1.9)	0.7	7	(11)	0.9	(0.4-2.1)	0.8	16	(16)	1.2	(0.6-2.4)	0.5
	CT or TT	341	(59)	118	60	1.0	(0.7-1.4)	0.91	106	(59)	1.0	(0.7-1.4)	0.8	30	(48)	0.7	(0.4-1.3)	0.3	62	(61)	1.1	(0.7-1.7)	0.7
							p-trend=	0.73				p-trend=	0.9				p-trend=	0.4				p-trend=	0.5
GPX1	CC	291	(46)	98	(47)	1.0	(ref)	.	95	(51)	1.0	(ref)	.	29	(42)	1.0	(ref)	.	51	(49)	1.0	(ref)	.
rs1050450	CT	284	(45)	89	(43)	0.9	(0.7-1.3)	0.7	75	(40)	0.8	(0.6-1.2)	0.3	32	(46)	1.1	(0.6-1.9)	0.7	47	(45))	0.9	(0.6-1.5)	0.8
	TT	61	(10)	22	(10)	1.1	(0.6-1.9)	0.8	16	(9)	0.8	(0.4-1.5)	0.5	8	(12)	1.5	(0.6-3.4)	0.4	7	(7)	0.7	(0.3-1.6)	0.4
	CT or TT	345	(54)	111	(53)	1.0	(0.7-1.3)	0.9	91	(49)	0.8	(0.6-1.2)	0.3	40	(58)	1.2	(0.7-2.0)	0.6	54	(51)	0.9	(0.6-1.4)	0.6
							p-trend=	0.9				p-trend=	0.3				p-trend=	0.4				p-trend=	0.4

NOS3	GG	300	(50)	94	(45)	1.0	(ref)	.	81	(45)	1.0	(ref)	.	33	(48)	1.0	(ref)	.	48	(46)	1.0	(ref)	.
rs1799983	GT	244	(41)	97	(47)	1.2	(0.9-1.7)	0.2	83	(46)	1.2	(0.9-1.8)	0.2	33	(48)	1.3	(0.8-2.2)	0.3	44	(42)	1.1	(0.7-1.7)	0.7
	TT	55	(9)	17	(8)	0.9	(0.5-1.7)	0.9	17	(9)	1.1	(0.6-1.9)	0.9	2	(3)	0.3	(0.1-1.4)	0.1	12	(11)	1.4	(0.7-2.8)	0.4
	GT or TT	299	(50)	114	(55)	1.2	(0.9-1.6)	0.3	100	(55)	1.2	(0.9-1.7)	0.3	35	(51)	1.1	(0.7-1.9)	0.7	56	(54)	1.1	(0.7-1.8)	0.5
							p-trend=	0.5				p-trend=	0.4				p-trend=	0.6				p-trend=	0.4
NOS3	TT	264	(43)	70	(36)	1.0	(ref)	.	75	41	1.0	(ref)		25	(40)	1.0	(ref)		43	(43)	1.0	(ref)	
rs2070744	CT	250	(41)	100	(51)	1.5	(1.0-2.1)	0.03	77	42	1.0	(0.7-1.5)	0.9	34	(54)	1.8	(1.0-3.2)	0.05	46	(46)	1.0	(0.6-1.6)	0.9
	CC	97	(16)	26	(13)	1.0	(0.6-1.6)	0.9	31	17	1.0	(0.6-1.6)	0.9	4	(6)	0.5	(0.2-1.5)	0.2	14	(14)	0.8	(0.4-1.5)	0.4
	CT or CC	347	(57)	126	(64)	1.3	(1.0-1.9)	0.09	108	59	1.0	(0.7-1.4)	0.9	38	(60)	1.4	(0.8-2.5)	0.2	60	(60)	0.9	(0.6-1.5)	0.8
							p-trend=	0.5				p-trend=	0.9				p-trend=	0.9				p-trend=	0.5
OGG1	CC	549	(59)	196	(56)	1.0	(ref)	.	148	(56)	1.0	(ref)	.	46	(52)	1.0	(ref)	.	76	(53)	1.0	(ref)	.
rs1052133	CG	324	(35)	136	(39)	1.1	(0.9-1.5)	0.3	98	(37)	1.1	(0.8-1.4)	0.6	39	(44)	1.4	(0.9-2.2)	0.2	59	(41)	1.3	(0.9-1.9)	0.2
	GG	58	(6)	15	(4)	0.6	(0.4-1.2)	0.2	17	(6)	1.1	(0.6-2.0)	0.7	4	(4)	0.7	(0.2-2.0)	0.5	9	(6)	1.2	(0.6-2.5)	0.7
	CG or GG	382	(41)	151	(43)	1.1	(0.8-1.4)	0.6	115	(44)	1.1	(0.8-1.4)	0.6	43	(48)	1.3	(0.8-2.0)	0.3	68	(47)	1.3	(0.9-1.8)	0.2
							p-trend=	0.9				p-trend=	0.6				p-trend=	0.7				p-trend=	0.2

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